CASE REPORT

Thrombolysis in submassive pulmonary embolism, prudent or puerile?

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SUMMARY

Pulmonary embolism (PE) remains one of the leading causes of cardiovascular mortality. The safety and efficacy of thrombolytic therapy using tissue-type plasminogen activator (tPA) for acute PE in clinical practice remain unclear. We describe a case of life-threatening submassive PE causing extreme refractory hypoxaemia, where thrombolysis was successfully administered. Current consensus suggests that patients with features of hemodynamic instability as a result of an acute PE, that is, massive PE, should receive thrombolysis. Patients, not in shock however, but with evidence of right-ventricular (RV) dysfunction echocardiographically, that is, submassive PE may also benefit. Serum troponin and brain-type natriuretic peptide have been suggested as biomarkers of RV injury that may identify a subset of submassive PE patients who may particularly benefit from thrombolytic therapy. The clinical response of this patient to thrombolysis is important, as it may identify a subgroup of patients with submassive PE who warrant this intervention.

BACKGROUND

Pulmonary embolism (PE) remains one of the leading causes of cardiovascular mortality. The wide range of reported death rates reflects heterogeneity in concomitant comorbidities and severity of PE. The safety and efficacy of thrombolytic therapy using tissue-type plasminogen activator (tPA) for acute PE in clinical practice remain unclear. Herein, we describe a case of life-threatening submassive PE causing extreme refractory hypoxaemia, where thrombolysis was successfully administered.

CASE PRESENTATION

A 63-year-old African American man, with a background of poorly controlled diabetes mellitus type 2 and hypertension presented with 1-week history of dyspnoea on exertion (The New York Heart Association Class-III). A week before he was hospitalised to another facility with severe hyperglycaemia after running out of his oral diabetes medications. During that hospitalisation, he developed a new-onset breathing difficulty. Ventilation/perfusion lung scan done at that time was indeterminate probability for PE and no further work up was pursued. After hospital discharge, his shortness of breath progressively got worse along with increasing fatigue. He denied leg swelling or pain, chest pain, palpitations, haemoptysis, lightheadedness or syncope. Physical examination revealed an anxious man who became dyspnoeic with minimal

exertion, was afebrile, heart rate was 82 beats/min, blood pressure 129/89 mm Hg and respiratory rate 24 breaths/min. The patient was hypoxaemic on room air (oxygen sats 84%) requiring high-flow oxygen through a non-rebreather mask. There was no obvious neck vein elevation, audible murmurs, loud P2 or right-ventricular (RV) lift.

INVESTIGATIONS

Laboratory data were remarkable for a positive cardiac troponin I level of 0.136 ng/ml (normal <0.012–0.034 ng/ml) and an elevated N-terminal pro-brain natriuretic peptide (NT-ProBNP) level of 4420 pg/ml (reference range, <600 pg/ml). ECG showed normal sinus rhythm, T wave inversion in anterior precordial leads (figure 1). Chest x-ray revealed no acute cardiopulmonary disease (figure 2). Contrast CT scan of the chest revealed extensive intraluminal filling defects throughout bilateral pulmonary arteries, involving all five lobes as well as the right and left main pulmonary arteries and saddle embolus present about the bifurcation of the left main pulmonary artery (figure 3). Transthoracic echocardiogram showed a free floating thrombus in right atrium swirling into the ventricle with every contraction, at high risk of distal embolisation and moderately dilated RV (figure 4).

TREATMENT

Given refractory hypoxaemia, unstable nature of the clot, patient refusal to undergo surgery for embolectomy and no absolute contraindications to tPA it was decided to proceed with thrombolysis. In total, 100 mg of tPA was administered over a 2 h period without any complications. Unfractionated heparin infusion was temporarily withheld during tPA administration and resumed without a loading dose when activated partial thromboplastin time (aPTT) was less than twice the upper limit of

Figure 1 ECG showing T wave inversion in anterior precordial leads.

To cite: Rehman A, Yousaf S, Chugh A. *BMJ Case Reports* Published Online First: [please include Day Month Year] doi:10.1136/bcr-2012-007549

Figure 2 Chest x-ray with no acute cardiopulmonary disease.

normal. We were able to be wean off oxygen within 2–3 h of thrombolysis.

OUTCOME AND FOLLOW-UP

A repeat echocardiogram after 24 h showed complete dissolution of the clot and mild improvement in RV size and TR jet (figure 5). Unfractionated heparin infusion was used as a bridge to anticoagulation with Warfarin. The patient was discharged home in a stable state after optimum International Normalised Ratio level was achieved.

DISCUSSION

PE remains a leading cause of mortality and morbidity around the world. As many as 300 000 deaths in the USA are reported from PE every year.^{1 2} Some reports suggest the death rate of PE in the first 3 months after diagnosis to be as high as 18%, exceeding the death rate for acute myocardial infarction.^{3 4} These are certainly underestimates of the true incidence of PE, since more than half of all PE cases are probably undiagnosed. Among survivors, approximately 2–5% of patients will die from recurrent pulmonary emboli during the initial 3–6 months of anticoagulant treatment and approximately 3% will have symptomatic, chronic thromboembolic pulmonary hypertension diagnosed during the next year.^{5 6}

Figure 3 CT chest revealing saddle embolus at the bifurcation of the main pulmonary trunk.

Figure 4 (A) Parasternal short-axis view with thrombus in right-ventricular cavity. (B) Apical four-chamber view showing the thrombus protruding from right atricular into right ventricular during diastole. (C) Severity of tricuspid regurgitation jet, before thrombolysis, estimated at 47 mm Hg.

Viewed primarily as a complication of hospitalisation for major surgery in the past, trials in contemporary era on patients hospitalised with a wide variety of acute medical illnesses and epidemiological studies have provided a better understanding of the risk factors for PE and helped to identify high-risk patients who could benefit from prophylaxis. Anderson and Spencer⁷ divided the risk factors for PE into patient related, for example, advanced age, obesity, hereditary or acquired hypercoagulable states, previous history of venous thromboembolism, etc, and setting-related risk categories, for example, reduced mobility due to any cause like travel, both air and ground, hospitalisation for medical or surgical illnesses, pregnancy, etc. Patient-related predisposing factors are usually permanent, whereas setting-related risk factors are more often temporary. However, the predictive values of these factors are not equal and PE can occur in patients without any identifiable predisposing factors.

Acute PE, where patients develop symptoms and signs immediately after obstruction of pulmonary vessels, is a spectrum of clinical syndromes with varying presentations and prognostic implications. In the literature, it has been conventionally divided into massive and submassive categories. Massive PE is defined as acute PE with sustained hypotension (systolic blood pressure <90 mm Hg for at least 15 min or requiring inotropic support,

Figure 5 (A) Parasternal short-axis view with thrombus not visible post-thrombolysis and improvement in right-ventricular size. (B) Apical four-chamber view showing complete resolution of the thrombus. (C) Improvement in severity of tricuspid regurgitation jet after thrombolysis, from 47 to 25 mm Hg.

not due to a cause other than PE, such as arrhythmia, hypovolaemia, sepsis or left-ventricular (LV) dysfunction), pulselessness or persistent profound bradycardia (heart rate <40 beats/min with signs or symptoms of shock).⁸ Whereas submassive PE represents the other end of the clinical spectrum of acute PE. A panoramic definition of submassive PE, provided by the Scientific Statement from the American Heart Association, is PE without systemic hypotension (SBP >90 mm Hg) but with either RV dysfunction or myocardial necrosis.⁸

RV dysfunction means the presence of at least one of the following:

- ▶ Echo: RV dilation (apical four-chamber RV diameter divided by LV diameter >0.9) or RV systolic dysfunction;
- ▶ CT: RV dilation (four-chamber RV diameter divided by LV diameter >0.9);
- ▶ BNP >90 pg/ml or N-terminal pro-BNP >500 pg/ml;
- ▶ ECG changes: new complete or incomplete right bundle branch block, anteroseptal ST elevation or depression or anteroseptal T wave inversion.

Myocardial necrosis is defined as either of the following: troponin I >0.4 ng/ml or troponin T >0.1 ng/ml.

With regard to pathophysiological events in submassive PE, there is abrupt rise in RV afterload, caused by increased pulmonary vascular resistance due to hypoxemic vasoconstriction, physical obstruction of the pulmonary arteries by thrombi and release of potent pulmonary arterial vasoconstrictors, resulting in acute RV pressure overload causing RV dilation, hypokinesis and tricuspid regurgitation.⁹ This brisk rise in after load cannot be tolerated by the normally thin-walled RV, which mainly acts as a conduit, and results in RV failure and cardiac arrest or death in more severe cases.

Administration of thrombolytics is considered a life-saving intervention in massive PE, it use still remains controversial in patients with submassive PE.¹⁰ Major reviews of thrombolysis in acute PE have mentioned severe hypoxaemia as a potential indication for thrombolysis. However, no guidelines address this issue with clarity. The main objective of our case report is to highlight the morbidity and mortality associated with submassive PE and point out to the paucity of data regarding the safe and effective use of fibrinolysis for this potentially life-threatening condition.

Thrombolysis, also known as the medical embolectomy, in patients with submassive PE will rapidly reverse haemodynamic compromise. It has been shown that at 24 h, thrombolytic therapy improves cardiopulmonary hemodynamics, that is, echocardiographic assessment of RV wall movement, mean pulmonary artery pressure, arteriovenous oxygen and pulmonary perfusion improvement.¹¹ A meta-analysis by Wan *et al*¹² in 2004, found that thrombolytic therapy compared with heparin was associated with a significant reduction in recurrent PE or death in trials that enrolled patients with major (haemodynamically unstable) PE (9.4% vs 19%; OR 0.45, 95% CI 0.22 to 0.92; number needed to treat=10) but not in trials that excluded these patients.

In 2002, the Management strategies and Prognosis of Pulmonary Embolism-3 Trial group compared rt-PA plus heparin and heparin alone in a double-blind trial of 256 PE patients with RV dysfunction but without hypotension or shock.¹³ The primary end point was death or escalation of therapy, defined as the need for catecholamine infusion, open-label thrombolysis, endotracheal intubation, cardiopulmonary resuscitation or emergency embolectomy. The primary end point occurred in 25% of patients treated with heparin alone compared with 10% of patients treated with rt-PA plus heparin ($p=0.006$). No intracranial haemorrhage occurred. However, of 2454 patients with PE, in International Cooperative Pulmonary Embolism Registry (ICOPER), 304 received thrombolysis, of whom 3% had intracranial bleeding.¹⁴ This contrast in bleeding rates points out how safety can vary markedly in the context of a controlled clinical trial compared with real-life clinical practice.

In a prospective study of 200 patients with submassive PE, echocardiography was performed at the time of diagnosis and after 6 months to determine the frequency of pulmonary hypertension.¹⁵ The estimated pulmonary artery systolic pressure at 6 months increased in 27% of patients receiving heparin alone. The median decrease in pulmonary artery systolic pressure was only 2 mm Hg in patients treated with heparin alone compared with 22 mm Hg in those treated with tPA plus heparin. Estimated pulmonary artery systolic pressure at follow-up did not increase in any of the patients treated with tPA.

Whether these observations translate into a meaningful reduction in mortality is still debated. Various randomised trials that compared thrombolytic therapy with anticoagulant therapy alone

in patients with acute PE and their meta-analyses suggest that thrombolysis may be associated with a reduction in mortality, but the strength of the evidence is weak.¹⁶ This is the purpose of the PEITHO study directed by Stavros Konstantinides and his team of researchers.¹⁷ Due for completion in early 2013, it will be a prospective, multicenter, international, randomised (1:1), double-blind comparison of thrombolysis with tenecteplase versus placebo in normotensive patients with confirmed PE, an abnormal right ventricle on echocardiography or CT and a positive troponin I or T test result.

To make things more complicated, so far there has been no unanimously approved risk prediction model for bleeding with thrombolytic therapy in PE patients and it is assumed that it is similar to patients with acute ST-elevation myocardial infarction. Of note, there is a slight difference in the dosing regimens for thrombolysis in PE-elevation and ST-elevation myocardial infarction. An analysis from the ICOPER, as pointed above, observed that the risk of intracranial haemorrhage may be as high as 3%.¹⁴ Numerous thrombolytic agents and regimens have been directly compared in randomised trials, but superiority of any thrombolytic agent or regimen over another has not been established. Studied regimens include tPA administration over 15 min or 2 h, urokinase administration over 2 or 24 h and streptokinase administration over 2, 12 or 24 h. The evidence suggests that shorter infusions (ie, ≤ 2 h) achieve more rapid clot lysis and are associated with lower rates of bleeding than longer infusions (ie, ≥ 12 h).¹⁶

The US Food and Drug Administration has approved tPA 100 mg administered as a continuous intravenous infusion over a 2-h period for treatment of acute massive PE. Nevertheless, tPA is often used off-label to treat submassive PE. All patients should be carefully screened for contraindications before being considered for thrombolysis. Unlike fibrinolysis in myocardial infarction, intravenous unfractionated heparin infusion is withheld during fibrinolysis in patients with acute PE. At the conclusion of the fibrinolytic infusion, the aPTT should be checked. Unfractionated heparin infusion should be restarted without a bolus when the aPTT is less than 80 s. If greater than 80 s, the aPTT should be rechecked every 4 h until it falls into the range at which heparin can be safely restarted.¹⁸ Major contraindications to fibrinolysis include intracranial mass; cerebrovascular event or neurosurgery within the prior 2 months; history of intracranial haemorrhage; recent major trauma; active or recent respiratory tract, gastrointestinal or genitourinary bleeding; severe uncontrolled hypertension; recent prolonged cardiopulmonary resuscitation; thrombocytopenia ($<50\,000$ platelets/ μL); acute pericarditis or pericardial effusion; ongoing suspicion of aortic dissection; and recent surgery, invasive procedure, or internal organ biopsy.^{8 16 18}

To date the safety and efficacy of catheter-directed delivery of the fibrinolytic agent directly into the pulmonary artery over peripherally administered fibrinolytic therapy has not been clearly established.^{19 20} Other interventional catheterisation techniques include mechanical fragmentation of thrombus with a standard pulmonary artery catheter, clot pulverisation with a rotating basket catheter, percutaneous rheolytic thrombectomy or pigtail rotational catheter embolectomy, but so far no randomised trials have evaluated interventional catheterisation techniques for PE.¹⁶ Catheter-assisted technique is an emerging advanced therapy for acute PE especially when full-dose fibrinolysis has failed or is contraindicated.¹⁸

Surgical embolectomy, involves a median sternotomy and cardiopulmonary bypass, is another management strategy for acute PE associated with hypotension. It is also suited for patients

with acute PE who require surgical excision of a right atrial thrombus, paradoxical arterial embolism or closure of a patent foramen ovale. Patients in whom thrombolysis has been unsuccessful it can be used as rescue procedure. Perioperative mortality for patients undergoing surgical embolectomy has declined in the recent years and it has been shown to be a safe and effective technique in the treatment of acute PE when performed by experienced surgeons.^{21 22} However no randomised trials or prospective observational studies have evaluated surgical embolectomy in patients with acute PE and evidence related to surgical embolectomy is sparse.¹⁶

In recently published guidelines by the American College of Chest Physicians, the use of systemically administered thrombolytic therapy has not been recommended in acute PE patients without hypotension (Grade 1C); however, in selected acute PE patients without hypotension and low risk of bleeding whose initial clinical presentation or clinical course after starting anticoagulant therapy suggests a high risk of developing hypotension administration of thrombolytic therapy is advisable (Grade 2C).¹⁶ While recommendations from the American Heart Association in their 2011 statement is that fibrinolysis may be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction or major myocardial necrosis) and low risk of bleeding complications (Class IIb; Level of Evidence C).⁸

A similar case was also reported by Piazza and colleagues in a 58-year-old woman with submassive PE and evidence of RV dysfunction and myocardial necrosis where thrombolysis was successfully administered after exclusion of all the absolute and relative contraindication.

As thrombolysis with subsequent heparin therapy carries greater risk of major haemorrhage than heparin alone, it is clearly very important to identify the subset of patients will benefit from this therapy. Current consensus suggests that patients with features of haemodynamic instability as a result of an acute PE, that is, massive PE, should receive thrombolysis. Patients, not in shock however, but with evidence of RV dysfunction echocardiographically, that is, submassive PE may also benefit. Serum troponin and brain-type natriuretic peptide have been suggested as biomarkers of RV injury that may identify a subset of submassive PE patients who may particularly benefit from thrombolytic therapy. The clinical response of this patient to thrombolysis is important, as it may identify a subgroup of patients with submassive PE who warrant this intervention. We also suggest that oxygenation status should be a component of future randomised controlled trials assessing thrombolysis in acute PE.

Learning points

- ▶ Pulmonary embolism (PE), the great mimicker of various diseases, can present in a variety of clinical settings and if included in the differential diagnosis, it needs to be confirmed or excluded using appropriate imaging studies.
- ▶ Thrombolysis, no doubt is the first-line treatment in patients with shock, but can be an equally useful tool in normotensive patients with PE and right ventricular dysfunction. Given the risks involved routine use of thrombolysis in patients with submassive PE is not recommended.
- ▶ While making treatment decisions for acute PE, pulmonary decompensation should also be taken into consideration.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Silverstein MD, Heit JA, Mohr DN, *et al.* Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585–93.
- 2 Heit JA, Cohen AT, Anderson FA, VTE Impact Assessment Group. Estimated annual number of incident and recurrent, nonfatal and fatal venous thromboembolism (VTE) events in the US (abstract). *Blood* 2005;106:267a.
- 3 Goldhaber SZ. Pulmonary embolism. In: Bonow RO, Mann DL, Zipes DP, *et al.* eds. *Braunwald's heart disease: a textbook of cardiovascular medicine*. 9th edn. Philadelphia: Saunders, 2011:1679–95.
- 4 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353:1386–9.
- 5 Douketis JD, Kearon C, Bates S, *et al.* Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998;279:458–62.
- 6 Pengo V, Lensing AW, Prins MH, *et al.* Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med* 2004;350:2257–64.
- 7 Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003;107:19–16.
- 8 Jaff MR, McMurtry MS, Archer SL, *et al.* Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123:1788–830.
- 9 Piazza G, Goldhaber SZ. The acutely decompensated right ventricle. *Chest* 2005;128:1836–52.
- 10 Piazza G, Goldhaber SZ. Acute pulmonary embolism, part II: treatment and prophylaxis. *Circulation* 2006;114:e42–7.
- 11 Dong B, Jirong Y, Wang Q, *et al.* Thrombolytic treatment for pulmonary embolism. *Cochrane Database Syst Rev* 2006;(2):CD004437.
- 12 Wan S, Quinlan DJ, Agnelli G, *et al.* Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation* 2004;110:744–9.
- 13 Konstantinides S, Geibel A, Heusel G, *et al.* Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med* 2002;347:1143–50.
- 14 Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet* 1999;353:1386–9.
- 15 Kline JA, Steuerwald MT, Marchick MR, *et al.* Prospective evaluation of right ventricular function and functional status 6 months after acute submassive pulmonary embolism: frequency of persistent or subsequent elevation in estimated pulmonary artery pressure. *Chest* 2009;136:1202–10.
- 16 Kearon C, Akl EA, Comerota AJ, *et al.* Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(2 Suppl): e419S.
- 17 Steering Committee. Single-bolus tenecteplase plus heparin compared with heparin alone for normotensive patients with acute pulmonary embolism who have evidence of right ventricular dysfunction and myocardial injury: rationale and design of the Pulmonary Embolism Thrombolysis (PEITHO) trial. *Am Heart J* 2012;163:33–8.e1.
- 18 Piazza G, Goldhaber SZ. Management of submassive pulmonary embolism. *Circulation* 2010;122:1124–9.
- 19 Verstraete M, Miller GA, Bounameaux H, *et al.* Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. *Circulation* 1988;77:353–60.
- 20 Gonzalez-Juanatey JR, Valdes L, Amaro A, *et al.* Treatment of massive pulmonary thromboembolism with low intrapulmonary dosages of urokinase: short-term angiographic and hemodynamic evolution. *Chest* 1992;102:341–6.
- 21 Leacche M, Unic D, Goldhaber SZ, *et al.* Modern surgical treatment of massive pulmonary embolism: results in 47 consecutive patients after rapid diagnosis and aggressive surgical approach. *J Thorac Cardiovasc Surg* 2005;129:1018–23.
- 22 Aklog L, Williams CS, Byrne JG, *et al.* Acute pulmonary embolectomy: a contemporary approach. *Circulation* 2002;105:1416–19.

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